REMARKS

Applicants have amended the present application to restate their claim to benefit of their provisional application 60/026,959. This amendment does not constitute new matter and its entry is respectfully requested.

Claims 15 – 27 were rejected under 35 U.S.C. § 112, first paragraph.

Applicants respectfully submit that this rejection should be withdrawn for the following reasons.

There appears to be some misunderstanding regarding the results provided in the present application. The Examiner, at page 5 of the Office Action, acknowledges, that the first and second examples using a β-Gal gene linked to an E2F responsive promoter, demonstrate that the E2F responsive promoter was highly reactive in a Glioma as compared to normal brain tissue. The Examiner then says, however, that the third example using an E2F promoter linked to a thymidine kinase (tk) gene shows no identifiable distinction between the action of the E2F promoter in normal tissues as compared to activity in a Glioma.

Applicants respectfully submit that the Examiner has misread the present application. As explained at pages 34 – 36, Applicants constructed two different vectors containing the thymidine kinase (tk) gene. The vectors differed in that in one, the tk gene was operably linked to the E2F promoter; whereas in the second, the tk gene was operably linked to the CMV promoter. These vectors were referred to as Ad.E2F1-tk and Ad.CMV-tk respectively. As explained in the paragraph bridging pages 34 – 35, **both** vectors were **effective** in treating the animal by taking advantage of the tk genes sensitizing the cells to ganciclovir.

However, as explained in the paragraph bridging 35 – 36, when one looked at the effect of the two vectors on normal brain tissue there was a substantial difference. When using the vector containing the CMV promoter there were extensive areas of local brain necrosis, inflammation and hemorrhage. See, particularly Figure 5C. In contrast, when the E2F responsive promoter was used there was no obvious tissue toxicity except that resulting from the local trauma of the stereotactic injection. This was indistinguishable from sham injected animals. Accordingly, the results demonstrate that the E2F responsive promoter while effective

in the glioma tissues did not harm the normal tissues, i.e. as claimed the use of the E2F promoter resulted in a selective expression of the gene in the malignant cells, which caused those malignant glioma cells to be killed by the tk gene.

These results also confirm in an *in vivo* model that the present invention works as claimed. This was confirmed by showing that the overall survival rate was identical between the animals injected under the control of CMV or the E2F responsive promoter, but that the animals lived significantly longer than animals in both control groups, $P<0.0001$. See Figure 5B. By contrast, the results also confirm that whereas the tk gene under control of the CMV promoter resulted in significant and substantial damage to normal brain tissue, the E2F promoter did not. Accordingly, contrary to what the Examiner has said, Example 3 was entirely confirmatory of the first two examples. The Examiner further indicated that presentation or results demonstrating the selective use of the E2F promoter in normal versus tumor tissue with another gene may provide convincing evidence of predictability. Applicants respectfully submit that the evidence submitted provided such proof.

Accordingly, applicants respectfully submit that the rejection under 35 U.S.C. § 112, first paragraph should be withdrawn.

Claims 15, 16, 19 – 23 and 25 – 27 were rejected under 35 U.S.C. §102(e) as being anticipated by U.S. Patent No. 5,885,833.

Applicants respectfully submit that this rejection should be withdrawn for the following reasons.

In the first instance, the 102(e) date of the `833 application is February 13, 1997, which is subsequent to Applicants' priority date under 35 U.S.C. 119(e). Accordingly, this reference does not constitute prior art for that purpose.

In addition, Applicants further note that the present claims are directed to a method that selectively targets cells by selectively expressing a gene in a malignant cell. Such a method is in no way taught by the `833 patent. For example, the `833 patent does not have a step such as that in claim 25 of determining whether a malignant cell expresses a sufficient level of E2F to cause expression of a gene operably linked to the E2F responsive promoter. Rather, that patent seeks to advantage of E2F effect in cell cycling. However, Applicants found that while E2F is normally expressed in a cell cycled dependent manner in **both** malignant and normal cells, we

have seen a selective expression in malignant cells was seen regardless of cell cycle. Accordingly, Applicants submit that one would not have expected such selectivity based upon reading the '833 specification and that the present method would not have been obvious. The Examiner's statement that ". . . the E2F promoter of US Pat No. 5,885,833 inherently contains all of the properties of the instant claimed E2F promoter," anticipates and ignores the fact that one cannot have anticipation without all steps being taught. Since the '833 did not actually carry out an *in vivo* example, it could not have made the observation. Thus, it had no reason to have the step contained therein. The fact that the application mentioned one can measure E2F activity in both normal and malignant cells does not mean that there is any teaching that one should do so as claimed. Accordingly, Applicants respectfully submit that for both reasons stated herein this rejection should be withdrawn.

Claims 15 – 23, and 25 – 27 were rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 5,885,833 in view of Raj et al. and WO 94/18992.

Applicants respectfully submit that this rejection should be withdrawn for the following reasons.

As discussed above, the '833 is not appropriate prior art against the present application because its 102(e) date is later than Applicants' priority date. In addition, Applicants further note that the deficiencies with the '833 cited above are not in any way overcome by the addition of Raj and WO 94/18992. The reason for this is that Raj merely discusses E2F whereas WO 94/18992 merely describes a different vector that can be used. There is nothing that would suggest that one substitutes the vector and creates claimed invention except the use of impermissible hindsight. Given the statements that are discussed regarding adenovirus vectors, there is actually a teaching away from getting selective expression.

Accordingly, the present rejection of the claims should be withdrawn for these additional reasons.

Claims 15 – 27 were also rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 5,885,883, Raj et al. and WO 94/18992 as applied to claims 15 – 23 and 25 – 27 above, and further in view of U.S. Patent 5,994,134.

Applicants respectfully submit that the reasons for withdrawing the rejection of the above claims is equally applicable here and they incorporate those arguments herein. The further

addition of the `134 for showing that cytotoxins were known, in no way suggests their applicability with other references. Indeed, without the knowledge from Applicants that one could selectively express such genes in a malignant but not a normal cell the skilled artisan would be concerned that there would be substantial harm to normal cells resulting from the use of such cytotoxins. Accordingly, Applicants respectfully submit that this rejection should be withdrawn for that additional reason.

In view of the foregoing applicants respectfully submit that all claims are in condition for allowance. Early and favorable action is requested.

Respectfully submitted,

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MARKED VERSION TO SHOW CHANGES MADE IN THE SPECIFICATION

IN THE SPECIFICATION

Page 1, Paragraph 1:

CROSS-REFERENCE TO RELATED APPLICATION

The present application claims benefit under 35 U.S.C. § 119(e) of U.S. Provisional Application No. 60/026,959 filed September 24, 1996.